PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 15270C-190-1	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2007/009499	International filing date *(day/month/year)* 27 July 2007 (27.07.2007)	Priority date *(day/month/year)*
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant ELAN PHARMA INTERNATIONAL LIMITED		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 02 February 2010 (02.02.2010)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Dorothée Mülhausen e-mail: pt01.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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SAN FRANCISCO, CA 94111

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	15 OCT 2007
Applicant's or agent's file reference 15270C-190-1	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US07/09499	27 July 2007 (27.07.2007)	18 April 2006 (18.04.2006)

International Patent Classification (IPC) or both national classification and IPC

IPC(8): **A61K 39/395**(2006.01)
USPC: 424/133.1,139.1

Applicant

ELAN PHARMA INTERNATIONAL LTD

1. This opinion contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450	01 October 2007 (01.10.2007)	Kimberly A. Ballard
Facsimile No. (571) 273-3201		Telephone No. 571-272-0500

Form PCT/ISA/237 (cover sheet) (April 2005)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US07/09499

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ on paper

☐ in electronic form

c. time of filing/furnishing

☐ contained in the international application as filed.

☐ filed together with the international application in electronic form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US07/09499

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 10-17,36-40 and 104-115

because:

☐ the said international application, or the said claim Nos. _____ relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 10-17,36-40 and 104-115 are so unclear that no meaningful opinion could be formed *(specify)*:

The claims are improper multiple dependent claims under PCT Rule 6.4(a).

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☐ no international search report has been established for said claims Nos. _____

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US07/09499

Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 3-4, 21-22, 27-35, 41-55	YES
	Claims 1-2, 5-9, 18-20, 23-26, 56-103	NO
Inventive step (IS)	Claims NONE	YES
	Claims 1-9, 18-35, 41-103	NO
Industrial applicability (IA)	Claims 1-9, 18-35, 41-103	YES
	Claims NONE	NO

2. Citations and explanations:

Please See Continuation Sheet

Supplemental Box
In case **the space in any of the preceding boxes is not sufficient.**

V. 2. Citations and Explanations:
Claims 1-9, 18-35 and 41-103 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

Claims 1-2, 5-6, 8, 18-20, 23-26 and 56-103 lack novelty under PCT Article 33(2) as being anticipated by US 6,787,637 B1 to SCHENK. Schenk discloses methods of treating Alzheimer's disease comprising administration of humanized antibodies that specifically bind to the N-terminus of amyloid-β (Aβ). Such antibodies include humanized versions of the monoclonal antibodies 3D6 (which binds to an epitope within Aβ1-5) and 10D5 (which binds to an epitope within Aβ3-6). The therapeutic antibodies are disclosed to bind to Aβ with a binding affinity greater than or equal to about 10^7, 10^8, 10^9, or 10^{10} M^{-1}. Schenk discloses that therapeutic dosages for antibody administration range from about 0.0001 to 100 mg/kg, and more usually 0.01 to 5 mg/kg host body weight. For a typical adult human weighing approximately 70 kg, the amount of administered antibody would be approximately 7-350 mg, and for an aged rat weighing approximately 0.55 kg (such as in an animal model of Alzheimer's disease), the dosage of administered antibody would range from 0.0055-2.75 mg. Thus, depending on the weight of the subject being administered the antibody, the dosages disclosed by Schenk encompass the instantly claimed antibody dosages.

The antibody may be administered on multiple occasions, with intervals between single dosages ranging from weekly to monthly to yearly. For example, an exemplary treatment regime is taught as administration of the antibody once per every two weekly (i.e., biweekly) or once a month or once every 3 to 6 months. Intervals can also be irregular as indicated by measuring blood levels of antibody to Aβ in the patient, and dosage can be adjusted to achieve a blood antibody concentration of 1-1000 μg/ml. The dosage and frequency of administration can vary depending on the half-life of the antibody in the patient, and whether the treatment is prophylactic or therapeutic in nature. For example, prophylactic applications may require treatment over longer periods of time than therapeutic applications, but in either case the treatment many be continued for years. Agents are disclosed as being administered by parenteral, intravenous, or subcutaneous routes.

Schenk also teaches that any of the disclosed diagnostic techniques, including assessment by cognitive testing such as Mini-Mental State Exam (MMSE), ADAS-COG, and MRI (see Example XVIII), may be used for evaluating and monitoring disease progression and/or response to treatment in patients who have been previously diagnosed with Alzheimer's disease. Accordingly, the teachings of Schenk anticipate instant claims 1-2, 5-6, 8, 18-20, 23-26 and 56-103.

Claims 3-4, 21-22, 27-35, 41-48 and 50-52 lack an inventive step under PCT Article 33(3) as being obvious over US 6,787,637 B1 to SCHENK in view of GILMAN et al. (2005) and CASEY et al. (2000). The teachings of Schenk are discussed above.

Supplemental Box
In case **the space in any of the preceding boxes is not sufficient.**

Gilman et al. teach the assessment of adverse effects for up to one year following a clinical trial in Alzheimer's patients receiving an immunotherapeutic agent (AN1792). Several commonly used cognitive and functional tests employed by Gilman et al. include ADAS-Cog, MMSE, Neuropsychological Test Battery (NTB), and MRI (see Abstract, p. 1553). Gilman discloses that infection (19%), headache (17.3%), diarrhea (9.7%), and encephalitis (6%) were among the more frequently reported adverse effects of the treated subjects (see pp. 1556-1557). Gilman notes that severe treatment-related adverse effects (AEs) occurred in 8% of patients who received active treatment (over half of which were associated with encephalitis) and in no patients who received placebo. Further, all 18 patients who reported meningoencephaltites received AN1792. Encephalitis, which is an inflammation of the brain, would therefore be of utmost importance to monitor for in patients receiving immunotherapy, and thus would obviate the instantly claimed posterior reversible encephalopathy syndrome (PRES) and/or vascular edema.

Casey et al. teach that PRES is typically characterized by headache, altered mental functioning, seizures, and visual loss associated with subcortical and cortical edema of a predominantly posterior distribution. Casey reports that Fluid-attenuated Inversion Recovery (FLAIR) MRI technology improves the ability to diagnose and detect subcortical and cortical lesions in PRES as compared to proton density- and T2-weighted spin-echo images (see Abstract, p. 1199). Thus, Casey recommends that FLAIR be used in patients with suspected PRES to allow more confident recognition of the often subtle imaging abnormalities.

It would have been obvious to the skilled artisan to monitor the efficacy of treatment of the antibody therapy disclosed by Schenk, such as by art-recognized cognitive tests such as NTB or magnetic resonance imaging technology such as FLAIR, particularly for assessment of adverse effects. Gilman teaches that encephalitis was a common adverse effect of Alzheimer's disease patients given immunotherapy, and the skilled artisan would thus expect that such would be the case with other types of immunotherapy. Accordingly, it would have been obvious to the skilled artisan to monitor for the occurrence of PRES or vascular edema in patients undergoing immunotherapy for Alzheimer's disease, such as by FLAIR technology. Thus, the combined teachings of the above references render obvious instant claims 3-4, 21-22, 27-35, 41-48 and 50-52.

Claims 1-2, 5, 9 and 56-103 lack novelty under PCT Article 33(2) as being anticipated US 2005/0118651 A1 to BASI et al. Basi et al. teach the use of the monoclonal antibody 12A11 for the treatment of Alzheimer's disease. Humanized versions of the 12A11 antibody are disclosed for therapeutic use in humans (see [0113]). The binding affinity of a humanized antibody is disclosed to be at least $3x10^9$ M^{-1} to $5x10^9$ M^{-1}. The dosage of administered antibody is taught to range from about 0.0001 to 100 mg/kg of host body weight, such as within the range of 0.5-115 mg/kg, and intermediate doses thereof (see [0224]). Doses can be administered daily, on alternative days, weekly, or according to any other schedule determined by empirical analysis. In therapeutic applications, the amount of administered antibody is disclosed as about 1 to 200 mg of antibody per dose, with dosages of from 5 to 25 being most commonly used. Both intravenous and subcutaneous administration of the therapeutic antibody are disclosed. Basi also teaches monitoring treatment in a patient, such as by measuring the level of administered antibody in the blood, so as to achieve an antibody blood concentration of 1-1000 µg/ml. Dosage and frequency of administration thus depend on the half-life of the antibody in the patient, and treatment regimes are adjusted accordingly. As such, the teachings of Basi et al. anticipate the invention of instant claims 1-2, 5, 9 and 56-103.

Claim 7 lacks novelty under PCT Article 33(2) as being anticipated by WYETH Annual Review 2005. The disclosure teaches the use of the monoclonal antibody, bapineuzumab (AAB-001), for the treatment of patients with Alzheimer's disease (see p. 16), thus anticipating instant claim 7.

Claims 49 and 53-55 lack an inventive step under PCT Article 33(3) as being obvious over WYETH Annual Review 2005 in view of GILMAN et al. (2005) and CASEY et al. (2000). The teachings of the references are discussed above. Accordingly, in view of the combined teachings of the above references it would have been obvious to the skilled artisan to monitor the effectiveness of bapineuzumab in Alzheimer's patients for the occurrence of encephalitis conditions such as PRES or vascular edema.